November 12, 2004

VIA HAND DELIVERY

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Scientific Considerations Related to Developing Follow-On Protein Products [Docket No. 2004N-0355]

Dear Sir or Madam:

Amgen Inc. ("Amgen") appreciates the opportunity to submit the following comments on the scientific considerations related to developing follow-on protein products. 69 FR 50387 (Aug. 16, 2004).

INTRODUCTION

Amgen is the world's largest biotechnology company and a pioneer in the development of biotechnology-derived protein products. Amgen's technical experience encompasses the fields of molecular and cellular biology, target discovery, safety assessment, therapeutic delivery, and biotechnology process development. Amgen has seven marketed products in the United States, including some of the most recognized biotechnology products, Epogen® (epoetin alfa), Neupogen® (filgrastim), and Enbrel® (etanercept). It is from this perspective that we comment on the science of follow-on biologics.1

1 We use the term "follow-on biologic" to capture the regulatory distinction between biological products regulated under the Public Health Service Act and drug products regulated under the Food, Drug, and Cosmetic Act.

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For this docket, the agency requested comments only on *scientific issues* related to follow-on biologics. As Amgen expressed in its testimony before the Senate Judiciary Committee,[2] the myriad legal, regulatory, and policy issues surrounding this subject also require careful consideration through a deliberate and transparent public process.

Amgen believes that in developing any regulatory paradigm for follow-on biologics, the following scientific principles must be adhered to: (1) follow-on biologics are unique products, and must be held to the same high standards of safety, purity, and potency as innovator products to ensure patient safety and well-being; (2) immunogenicity and other adverse events present a serious concern for all biologics and should be studied pre-approval through controlled clinical trials and monitored with robust post-approval surveillance; and (3) follow-on biologics cannot be considered therapeutically equivalent to the innovator product and will necessarily require unique labeling. If these fundamental principles are maintained, and innovator rights are fully respected, we believe that through a sound public process, Congress, the Food and Drug Administration (FDA), patients, and the industry can begin to develop a sensible approach to the approval of safe and effective follow-on biologics to provide additional treatment options to patients and health care professionals.

We also recognize the potential need, for purposes of this discussion, to distinguish between protein products, on the one hand, and other biologic-like products, including vaccines and gene therapy, on the other hand. Therefore, it may be appropriate to adopt the consensus term "follow-on protein biologics." At this time, however, we will continue to use the shortened phrase "follow-on biologics."

2 Statement of David Beier, Senior Vice President Global Government Affairs, Amgen, before the Committee on the Judiciary, United States Senate, June 23, 2004; *available at* http://judiciary.senate.gov/testimony.cfm?id=1239&wit_id=3631.

COMMENTS

Amgen agrees generally with the positions articulated by PhRMA and BIO at the stakeholder meeting and with their written submissions to this docket. In any discussion of follow-on biologics, it is critical to recognize the impact of the manufacturing process on the safety, purity, and potency of biological products and the limitations of current analytical means for determining the identity and biological activity of these products. These include limitations relating to product characterization, product and process impurities, and the difficulties in determining tertiary structure. As complex mixtures of heterogeneous proteins and impurities, biological products are difficult to characterize with precision, and impossible to characterize with certainty. Because of these limitations, we do not think it is currently possible to demonstrate the absolute identity of a follow-on biologic with that of the reference innovator product.[3] Therefore, the manufacturer of any such product will need to establish its own unique safety and efficacy profile through appropriate preclinical and clinical testing. Each follow-on biologic also would need to have its own unique labeling with full tabulation of unexpected adverse events, including immunogenicity assessments, so that physicians would have the appropriate knowledge needed to treat patients safely and effectively.

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3 This concept is also supported by a recent paper by Dr. Schellekens, which demonstrates that so-called "generic" epoetin alfas from other parts of the world are qualitatively and quantitatively distinct from the epoetin alfas approved in the United States and Europe. For example, the "generic" versions represent different glycosolated species, with corresponding differences in *in vitro* and *in vivo* activity. H. Schellekens, *Biosimilar epoetins: how similar are they?*, EJHP, Scientific Section (March 2004) at 43-47.

Comment 1: The potential for antibody response to biological products is fundamentally different than with small-molecule drugs, making clinical study necessary for all biological products.

Toxicity with proteins often presents differently than with small-molecule pharmaceutical drugs. Preclinical studies with biologics do not always predict adverse events in humans. Each biologic manufacturer must therefore supplement the original label with multiple changes that augment the safety database profile throughout the life of the product. The safety data may come from phase IV commitment studies, spontaneous adverse event reports to the manufacturer and/or FDA and, in many cases, studies that specifically examine safety questions that may arise during the pre-market and post-market phases.

In addition to expected and unexpected adverse events related to the pharmacology of the product, large-molecule products raise the potential for unwanted antibody responses whose consequences are unpredictable. These immunogenic responses in patients can be triggered by low level species such as product-related or process-related impurities. They may also be triggered by the product itself, because large-molecule protein products, unlike small-molecule drugs, are large enough to be recognized by the body's immune system.

Furthermore, the way in which unwanted immunogenicity may present in different patients is unpredictable and varied. For example, some patients may produce neutralizing antibodies that block the effectiveness of the body's own endogenous molecule, while others may produce antibodies that bind to the wrong receptor and perturb otherwise healthy tissue. Other patients may produce antibodies that appear to be without consequence, while some may produce antibodies that cause a dramatic increase or decrease in the administered protein's clearance and/or potency. Even among proteins with identical amino acid sequences,

immunogenicity of the product can vary dramatically. Because of this variety of potential immune responses, which may affect many different biological functions and the safety, dosing, clearance, and efficacy of the product, it is essential to investigate the safety and immunogenicity of any protein product with appropriate preclinical and clinical testing pre-approval, and robust pharmacovigilance post-approval.

Preclinical evaluation for toxicity and immunogenicity is the important first step in this investigative process. Like other products regulated by FDA, *in vivo* testing of a therapeutic protein begins with preclinical animal studies, with considerable attention paid to the early detection of an antibody response, in addition to on-target and off-target toxicities. Importantly, however, an absence of immunogenicity in animals does not ensure that immunogenicity will not present later in humans. Thus, preclinical toxicity testing in animals is an essential but imperfect first step in the development of any protein product.4

In the earliest phase of clinical testing, it is important to assess the half-life and clearance of the protein, in addition to monitoring for any signals of immunogenicity. Unlike with small-molecule drugs, pharmacokinetic effects can vary greatly from product to product within the same protein class. For example, six companies manufacture FDA-approved versions of human growth hormone – one of the oldest and best-understood biotechnology products. Although each of these products has the same number of amino acids and very similar molecular weights, the

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4 *See* FDA/ICH Guideline for Industry, S6 *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997) at 3.6 ("Antibody responses should be characterized (e.g., titer, number of responding animals, neutralizing or non-neutralizing) and their appearance should be correlated with any pharmacological and/or toxicological changes.").

terminal elimination half-life of each product varies tremendously, from 1.75 to 10 hours.5 This is not a trivial distinction, because the clearance of a protein product can impact the effectiveness of the product, as well as the body's potential immune response to it. Such large variation in pharmacokinetic data for different versions of the same basic protein not only renders those products therapeutically nonequivalent, but also raises potential safety concerns if those products are dosed at the same level.

As clinical testing progresses to larger-scale studies, which often involve at least several hundred, if not several thousand, subjects, innovator companies continue to evaluate possible safety risks, with specialized attention to the potential antibody response. This can be complicated, because almost *every* protein or monoclonal antibody administered to humans will cause some sort of immunogenic response in some, if not most, patients. Furthermore, as noted above, the same protein can cause several different kinds of antibody responses when administered to different patients, and these responses cannot be predicted through analytical or preclinical testing alone.

The data and experience derived from the development of any one protein therapy – including toxicity studies in animals, comprehensive clinical trials in humans, pharmacovigilance monitoring, and the relationship between the product and a particular manufacturing process – cannot merely be transferred to other versions of the same protein. Instead, we believe that no two biological products are identical, and that the unique safety risks associated with biological products compels certain standards regarding clinical study.

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5 Lisa J. Raines, *Bad Medicine: Why the Generic Drug Regulatory Paradigm is Inapplicable to Biotechnology Products*, J Bioloaw and Business, 2002; 5(1): 6-13 at 9.

With regard to safety, we recommend that there be appropriate preclinical safety studies using as guidance the ICH S6 Guideline, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. We also recommend that any approval be supported by appropriately sized clinical trials, and we recommend that the ICH Guideline, *Extent of Population Exposure to Assess Clinical Safety*, be used as an initial guide in determining the scope and duration of these trials. This Guideline recommends patient exposure of 100 for 12 months, 300-600 for six months, with a total exposure of about 1500 patients. The guideline acknowledges that these numbers should be evaluated with respect to the specific product and indication. A thorough assessment of immunogenicity should be provided as part of the safety database for the follow-on product. If antibodies are identified, they should be fully characterized, including an assessment of neutralizing ability, and the affected patients should be monitored until the antibodies resolve. Finally, robust post-approval pharmacovigilance, including continued monitoring for immunogenicity, as well as other adverse events, should also be implemented. It is essential to follow the patients for an extended period of time to determine whether an immune response will occur and what the clinical and safety effects of that response are.

With regard to efficacy, any approval should be supported by bioequivalence studies and controlled trials to establish efficacy, using either well-accepted surrogate markers or clinical endpoints. For products with multiple indications, each indication should be supported by appropriate data, especially for those indications where the underlying biology or mechanism of action is unclear.

Comment 2: When innovators make significant manufacturing changes, they confirm safety and efficacy of the product through clinical testing.

From our own experience, Amgen knows that significant changes in the manufacturing process have the potential to lead to significant differences in the resultant protein. However, we have found it is possible to qualify *discrete* changes to the manufacturing process using a combination of analytical data that include process evaluations, comparison of product release data with historical data, and the use of additional analytical characterization to demonstrate comparability. These types of changes are relatively defined and generally encompass discrete changes to a unit operation, such as site changes or scale-up changes that are not associated with any fundamental changes in the overall process chemistry.

It is more difficult, however, to qualify *significant* changes in the process that affect the fundamental production technology, such as significant changes to the starting source cell bank. Amgen frequently qualifies such changes using additional product characterization that includes preclinical studies, pharmacokinetic analysis, and clinical studies to confirm the safety and efficacy of the product. It is important to note that the extent and types of studies are dependent on the particular product, its intended use, and what is known about its expected and unexpected adverse event profile. Preclinical and/or clinical data may be warranted even when there are no obvious differences in the analytical profile of the product because of the significance of the change and our evaluation of potential toxicities associated with the product. Thus, as part of a comparability determination and consistent with FDA's guidance, innovator companies

frequently will conduct clinical studies to confirm the safety and potency of an approved product after making significant manufacturing changes.6

Even to the extent that these types of changes are similar in kind to those that may be associated with a second manufacturer, an important difference remains. The second manufacturer would not have the benefit of the process history of the innovator, or the use of the proprietary reference standards, analytical methods, and assays used by the innovator. In such a case, the second or follow-on manufacturer should provide its own unique preclinical data and clinical data to establish safety and efficacy. This requirement is consistent with the extent of data generated by innovators to confirm safety and efficacy after implementing significant changes in manufacturing.

The goal of an approval process for follow-on biologics is to take advantage of the experience already developed by innovators, and the regulatory experience associated with the use of a particular product class. However, biotechnology products are simply too sensitive to their particular manufacturing processes, and immune responses too variable and unpredictable, to allow a follow-on sponsor to rely exclusively on the innovator's preclinical or clinical research to establish the safety and effectiveness and labeling of its own unique product.

Comment 3: Innovator products and follow-on biologics cannot be considered therapeutically equivalent.

As discussed above and in the comments of BIO and PhRMA, proteins cannot be characterized and duplicated in the same way as small-molecule drugs. Thus, follow-on biologics can never be considered "true generic copies" of the innovator products. The current

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6 *See* Genentech Citizen Petition (April 8, 2004) at 14, 18 (discussing clinical trials conducted with Raptiva® following a manufacturing change for that product).

paradigm for determining therapeutic equivalence and substitutability of generic drug products, therefore, is not sufficient to assure the safety, purity and potency of protein products. In addition, given the diversity of immune response and the degree to which proteins are tied to their manufacturing process and other variables, we suggest the need for original labeling for all of these products, based on the clinical experience from the use of each product.

Decisions on appropriate treatment of disease remain the responsibility of the prescribing physician in discussion and consultation with each individual patient. The physician depends on accurate, current, and specific information contained in the label to prescribe products to patients in a safe and effective manner. Each biologic, innovator or follow-on, should have a unique safety database profile to be weighed by the patient and physician when presented with a choice of potential therapies. For example, a patient never treated with a particular biologic protein might need to be treated differently than a patient who had received treatment with an innovator biologic and was considering treatment with a follow-on biologic. This would be an especially critical consideration if a patient treated with a particular biologic therapy were to suffer adverse events severe enough that alternative therapy would be considered.

Accurate information on potency and efficacy is also critical for the physician and patient. For example, dosing is often calculated in proportion to the weight of the individual. Any changes in potency that might be introduced by the follow-on manufacturing process would need to be studied in clinical trials and described in the follow-on biologic label, so that appropriate dosing could be prescribed by the physician.

Lastly, as unique products, follow-on biologics should not carry the identical non-proprietary name as the innovator, but instead should be distinguished by a unique USAN name,

assigned by the United States Adopted Names Council. At minimum, follow-on products should be assigned unique suffixes to reflect differences caused by glycosylation and associated with a different manufacturer.

CONCLUSION

In conclusion, we reiterate the core principles that should guide discussions about possible approvals of follow-on biologics. First, any such process must be transparent, public, and science-based so that the risks we have highlighted may be fully debated by the medical, scientific, and patient communities. This process should include a period of public comment regarding the appropriate approval standards for specific products or product classes. For example, it appears certain that preclinical and clinical data will be required to establish safety and efficacy of a follow-on biologic, but it is not clear what amount of data would be necessary or how information in the public domain can be leveraged to facilitate development. We recommend that the National Academy of Sciences' Institute of Medicine and other respected science-based organizations be included in this process.

Second, the potential risks of immunogenicity are very significant and can be devastating to patients in the most extreme circumstances. Therefore, the risk of immunogenicity should be assessed for each product and characterized with appropriate pre-approval clinical data to protect patients from undue risk when the product is introduced into the marketplace. Of course, robust safety monitoring must continue post-approval, but a significant attempt (via appropriately sized, well-designed clinical trials) must be made to detect and assess immune responses before approval. Any truncation in the breadth or duration of these trials will decrease the opportunity to detect immunogenicity warnings.

Third, because proteins cannot be characterized and duplicated in the same way as small-molecule drugs, follow-on biologics can never be considered "true generic copies" of the innovator products, and cannot be deemed therapeutically equivalent to the innovator products.

With these principles in mind, Amgen believes it is possible to discuss the feasibility of developing an approval pathway for follow-on biologics. Amgen believes that there is no barrier, in the abstract, to the development of follow-on products to provide patients and healthcare providers with more treatment options, so long as full respect for innovators' intellectual property, such as patents, trade secrets, and confidential commercial information, is maintained and patients receive safe and useful products. However, we believe that extensive public discussions are needed regarding which preclinical and clinical requirements could be abridged for follow-on biologics, while still satisfying the approval standards of safety, purity and potency.

FOR: Kenneth Seamon, Ph.D.
Vice President, Regulatory Affairs